Refractory colorectal cancer patient derived MicroOrganoSpheres (MOS)™ enables correlation of targeted therapy combination response with clinical outcomes

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Background
Metastatic colorectal cancer (CRC) patients who have become resistant to standard-of-care (SOC) treatments are often put on targeted therapies, including experimental drugs still in clinical trials. However, patients with targeted mutations still often do not respond to the targeted therapies alone, hence it remains a critically unmet need to explore potential combinatorial regimens that will enhance the efficacy.

Methods
We performed a high-throughput screen using MicroOrganoSpheres (MOS)™ derived from metastatic refractory patients to correlate with clinical outcomes and explore alternative combinations that might benefit the patients. Biopsies from metastatic CRC patients who became resistant to SOC and were about to receive targeted therapies in clinical trials were molecularly profiled and implanted into immunodeficient mice to generate patient-derived xenografts (PDX). MOS generated from PDX were treated with drug combination titrations based on physiologically relevant concentrations. Live/dead staining was performed on day 5 post drug dosing and quantified via high-content imaging and a custom image analysis pipeline. Relative viability per drug concentration was calculated in triplicate as percent live (live / all fluorescence signal) and normalized to an empty control.

Results
Figure 1. Scheme of targeted drug screen platform using MOS technology.

Table 1. Refractory CRC patient with experimental drugs in clinic

<table>
<thead>
<tr>
<th>PDX ID</th>
<th>Mutation</th>
<th>Tissue source</th>
<th>Post treatment immunotherapy</th>
<th>SOC</th>
<th>Response</th>
<th>RECIST %</th>
</tr>
</thead>
<tbody>
<tr>
<td>B8239</td>
<td>KRAS G12C</td>
<td>Liver</td>
<td>MRTX1133 + Trametinib</td>
<td>Panitumumab + Cetuximab + Nivolumab</td>
<td>Progression</td>
<td>33%</td>
</tr>
<tr>
<td>B8281</td>
<td>WT</td>
<td>Liver</td>
<td>MRTX1133 + Trametinib</td>
<td>Panitumumab + Cetuximab + Nivolumab</td>
<td>Progression</td>
<td>33%</td>
</tr>
<tr>
<td>B8239</td>
<td>KRAS G12C</td>
<td>Liver</td>
<td>MRTX1133 + Trametinib</td>
<td>Panitumumab + Cetuximab + Nivolumab</td>
<td>Progression</td>
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<tr>
<td>B8293</td>
<td>BRAF V600E</td>
<td>Liver</td>
<td>MRTX1133 + Trametinib</td>
<td>Panitumumab + Cetuximab + Nivolumab</td>
<td>Progression</td>
<td>33%</td>
</tr>
</tbody>
</table>

Figure 2. MOS derived from refractory CRC patient with KRAS G12C mutant response to experimental drugs (Amgen vs. Mirati). Response curve is plotted from MOS dosed with AMG510 or MRTX1494 in combination with Trametinib (A, B) in 5-dose titrations. X-axis represents AMG510 titrations: 1/4096/800x, 1/256/800x, 1/16/16x.

Figure 3. MOS drug response box plot graphs show correlation with clinical outcomes from refractory patients with no mutations. Response curve is plotted from MOS dosed with Panitumumab (A, B) in 5-dose titrations. X-axis represents Panitumumab titrations: 1/4096/800x, 1/256/800x, 1/16/16x.

Figure 4. MOS drug response box plot graphs show correlation with clinical outcomes from refractory patients with BRAF V600E mutations. Response curve is plotted from MOS dosed with Encorafenib with Cetuximab (A, B) in 5-dose titrations. X-axis represents Encorafenib titrations: 1/4096/800x, 1/256/800x, 1/16/16x.

Conclusion
Refractory patients may benefit from a MOS™-based high-throughput screen assay to select the optimal combination regimen containing targeted therapy.

Future Directions
- SOC or targeted drug screen response in MOS from CRC patient correlates with clinical outcome.
- Use MOS drug response platform to predict patient outcome.

References